centronuclear myopathy

Centronuclear myopathy is a condition characterized by muscle weakness (myopathy) and wasting (atrophy) in the skeletal muscles, which are the muscles used for movement. The severity of centronuclear myopathy varies among affected individuals, even among members of the same family.

People with centronuclear myopathy begin experiencing muscle weakness at any time from birth to early adulthood. The muscle weakness slowly worsens over time and can lead to delayed development of motor skills, such as crawling or walking; muscle pain during exercise; and difficulty walking. Some affected individuals may need wheelchair assistance as the muscles atrophy and weakness becomes more severe. In rare instances, the muscle weakness improves over time.

Some people with centronuclear myopathy experience mild to severe breathing problems related to the weakness of muscles needed for breathing. People with centronuclear myopathy may have droopy eyelids (ptosis) and weakness in other facial muscles, including the muscles that control eye movement. People with this condition may also have foot abnormalities, a high arch in the roof of the mouth (high-arched palate), and abnormal side-to-side curvature of the spine (scoliosis). Rarely, individuals with centronuclear myopathy have a weakened heart muscle (cardiomyopathy), disturbances in nerve function (neuropathy), or intellectual disability.

A key feature of centronuclear myopathy is the displacement of the nucleus in muscle cells, which can be viewed under a microscope. Normally the nucleus is found at the edges of the rod-shaped muscle cells, but in people with centronuclear myopathy the nucleus is located in the center of these cells. How the change in location of the nucleus affects muscle cell function is unknown.

Frequency

Centronuclear myopathy is a rare condition; its exact prevalence is unknown.

Genetic Changes

Centronuclear myopathy is most often caused by mutations in the *DNM2*, *BIN1*, or *TTN* gene. The proteins produced from the *DNM2* and *BIN1* genes are involved in endocytosis, a process that brings substances into the cell. The protein produced from the *BIN1* gene plays an additional role in the formation of tube-like structures called transverse tubules (or T tubules), which are found within the membrane of muscle fibers. These tubules help transmit the electrical impulses necessary for normal muscle tensing (contraction) and relaxation. The protein produced from the *DNM2* gene also regulates the actin cytoskeleton, which makes up the muscle fiber's structural

framework. *DNM2* and *BIN1* gene mutations lead to abnormal muscle fibers that cannot contract and relax normally, resulting in muscle weakness.

The *TTN* gene provides instructions for making a protein called titin that is an essential component of muscle fiber structures called sarcomeres. Sarcomeres are the basic units of muscle contraction; they are made of proteins that generate the mechanical force needed for muscles to contract. *TTN* gene mutations decrease or alter titin's activity in muscle fibers. It is unclear how these mutations lead to centronuclear myopathy, but it is likely that the altered protein cannot interact with other proteins in the sarcomere, leading to dysfunction of the sarcomere. Abnormal sarcomeres prevent muscle fibers from contracting and relaxing normally, resulting in muscle weakness.

Some people with centronuclear myopathy do not have identified mutations in the *DNM2*, *BIN1*, or *TTN* genes. Mutations in other genes associated with this condition are found in a small percentage of cases. Some males with signs and symptoms of severe centronuclear myopathy may have a condition called X-linked myotubular myopathy, which is similar to centronuclear myopathy, and is often considered a subtype of the condition, but has a different genetic cause. In some people with centronuclear myopathy, the cause of the disorder is unknown. Researchers are looking for additional genes that are associated with centronuclear myopathy.

Inheritance Pattern

When centronuclear myopathy is caused by mutations in the *DNM2* gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered *DNM2* gene in each cell is sufficient to cause the disorder. Rarely, *BIN1* gene mutations that are inherited in an autosomal dominant pattern can cause centronuclear myopathy.

Centronuclear myopathy caused by *TTN* gene mutations and most cases caused by *BIN1* gene mutations are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other cases of centronuclear myopathy that are not caused by these genes are typically inherited in an autosomal recessive manner, although some follow an autosomal dominant pattern.

Other Names for This Condition

- CNM
- myopathy, centronuclear

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Autosomal recessive centronuclear myopathy
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0410204/
- Genetic Testing Registry: Myopathy, centronuclear
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN221282/
- Genetic Testing Registry: Myopathy, centronuclear, 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1834558/
- Genetic Testing Registry: Myopathy, centronuclear, 4
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3553709/
- Genetic Testing Registry: Myopathy, centronuclear, 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN218417/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Muscle Disorders
  https://medlineplus.gov/muscledisorders.html

Genetic and Rare Diseases Information Center

- Centronuclear myopathy
  https://rarediseases.info.nih.gov/diseases/101/centronuclear-myopathy

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Congenital Myopathy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Congenital-Myopathy-Information-Page

Educational Resources

- CLIMB: Myotubular Myopathy Information Sheet
  http://www.climb.org.uk/IMD/Mike/Myotubular%20Myopathy.pdf
- Disease InfoSearch: Myopathy, centronuclear, 1
  http://www.diseaseinfosearch.org/Myopathy%2C+centronuclear%2C+1/8947
- MalaCards: myopathy, centronuclear
  http://www.malacards.org/card/myopathy_centronuclear
- Merck Manual Consumer Version: Congenital Myopathies
  http://www.merckmanuals.com/home/children-s-health-issues/muscular-dystrophies-and-related-disorders/congenital-myopathies
- Orphanet: Autosomal dominant centronuclear myopathy
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=169189
- Orphanet: Autosomal recessive centronuclear myopathy
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=169186
- Orphanet: Centronuclear myopathy
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=595
- Washington University, St. Louis: Neuromuscular Disease Center: Centronuclear Myopathy, Autosomal Dominant
  http://neuromuscular.wustl.edu/syncm.html#cnmdyn2
- Washington University, St. Louis: Neuromuscular Disease Center: Centronuclear Myopathy, Autosomal Recessive
  http://neuromuscular.wustl.edu/syncm.html#arcnm

Patient Support and Advocacy Resources

- CLIMB: Children Living with Inherited Metabolic Diseases
  http://www.climb.org.uk/
- Joshua Frase Foundation
  http://www.joshuafrase.org/life-with-cnm-mtm.php
- Muscular Dystrophy Association
  https://www.mda.org/disease/inherited-and-endocrine-myopathies/types/centronuclear-myotubular

- Muscular Dystrophy UK: Muscular Dystrophies
  http://www.musculardystrophyuk.org/about-muscle-wasting-conditions/muscular-dystrophies/
- Myotubular Trust
  http://www.myotubulartrust.com/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/centronuclear-myopathy/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22centronuclear+myopathy%22+OR+%22Myotubular+Myopathy%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Myopathies,+Structural,+Congenital%5BMAJR%5D%29+AND+%28centronuclear+myopathy%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D

OMIM

- MYOPATHY, CENTRONUCLEAR, 1
  http://omim.org/entry/160150
- MYOPATHY, CENTRONUCLEAR, 2
  http://omim.org/entry/255200
- MYOPATHY, CENTRONUCLEAR, 4
  http://omim.org/entry/614807
- MYOPATHY, CENTRONUCLEAR, 5
  http://omim.org/entry/615959

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